

# Models cannot predict future outbreaks: A/H1N1 virus, the paradigm

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22    **Abstract**

23    Evolution of the industrialized society had led to a risk management policy in many domains.  
24    Assessment of health care risk in the case of infectious diseases often includes mathematical  
25    models. Results of modelling were used in France to design emergency plans against flu  
26    pandemic. We believe that models cannot predict the features of the future outbreaks  
27    because the intrinsic properties of an emergent pathogen and the ecosystem in which it is  
28    developing are very complex. Of course, prediction of future outbreaks is not possible  
29    without using models, but we think that it is an illusion to presently believe that emerging  
30    phenomenon can be anticipated by using only prediction from models. The recent pandemic  
31    caused by the novel A/H1N1 virus has confirmed the unpredictability of infectious diseases.  
32    The rapid evolution in several domains such as antimicrobial therapeutics, vaccine and  
33    hygiene conditions make comparison with past pandemics hard. The adherence of  
34    populations to prevention measures and immunisation campaigns are unpredictable. In  
35    addition, the presentation of pessimistic models is deleterious. They impress governments  
36    and provoke fears. There is a striking necessity to develop the number and the capacities of  
37    sentinel centres to take and adapt decisions based on timely available scientific information.

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39 Evolution of society had led to a risk management policy in many domains. The  
40 assessment of health care risk in infectious diseases, especially concerning future epidemics,  
41 often includes mathematical models which tentatively predict *in silico* the burden of the  
42 future outbreaks such as attack rate, dissemination, morbidity or mortality. Currently,  
43 models are designed to run with different scenarios, and probabilistic methods allow testing  
44 their performance in a number of situation. But the question asked by physicians, scientists  
45 and in fact everyone is “how many people will die, how many will be hospitalized?”. Such  
46 predictions from models were used in France to design the emergency plan against flu  
47 pandemic [1]. We believe that models cannot predict with acceptable accuracy the features  
48 of the future outbreaks because the intrinsic properties of an emergent pathogen and the  
49 ecosystem in which it is developing are very complex and unstable. Of course, prediction of  
50 future outbreaks is not possible without using models, but we think that it is an illusion to  
51 presently believe that emerging phenomenon can be anticipated by using only prediction  
52 from models. The recent pandemic caused by the novel A/H1N1 virus has confirmed the  
53 unpredictability of infectious diseases.

54 Seasonality of respiratory infections is a well-known phenomenon in temperate  
55 regions. Flu has long been associated with cold season, and the word "Influenza" comes  
56 from “influenza di freddo” in Italian that means “cold influenced”. A marked peak of  
57 respiratory infections occurs during cold winter months. Several mechanisms have been  
58 proposed to explain it, such as seasonal environmental changes (temperature humidity...),  
59 seasonal host-behaviour changes and seasonal changes in host physiology (melatonin,  
60 vitamin D...) [2-4]. However there is still no clear understanding of this phenomenon. In  
61 contrast, disease seasonality is less defined in tropical regions where a background of  
62 influenza cases is observed throughout the year on top of which epidemics occur at  
63 intermediate months between the influenza season in temperate countries of the Northern  
64 and Southern hemispheres [4]. On the top, none of yet proposed determinants can explain  
65 why the four last pandemics of influenza (1918, 1957, 1968, and 2009) did not initiate during  
66 the cold season.

67 Interference between several respiratory viruses affecting the spread of influenza  
68 was recently described in Europe and drastically modified the dynamics of the outbreak [5-  
69 6]. In France and in Sweden, an epidemic of rhinovirus infections occurred after the start of

70 school year, and delayed the onset of the A/H1N1 pandemic. We also observed in Marseille  
71 that the epidemic of Respiratory Syncytial Virus bronchiolitis, which happens usually just  
72 before the seasonal flu epidemic, occurred later in the season, just after that the A/H1N1  
73 pandemic started to decline. In addition interference between several Influenza viruses  
74 remains not properly known: at the beginning of the A/H1N1 pandemic, nobody was able to  
75 predict whether seasonal influenza strains (H3N2 and H1N1) would still provoke an epidemic  
76 wave or not.

77 In certain groups of population, the presence of cross-reactive antibodies against a  
78 new pandemic strain of influenza can heavily affect viral dissemination and therefore impact  
79 on the epidemiologic characteristics of the pandemic (total number of cases, age of the  
80 cases, number of severe cases, number of deaths, death rate, length of the phenomenon...) and seems unpredictable. The fact that the elderly were partially protected against the novel  
81 A/H1N1 [7-9] explains that the novel A/H1N1 virus infected mostly young people. In  
82 addition, at-risk groups may not be the same as for seasonal flu. For example, obesity was an  
83 undisputable independent risk factor of severity and lethality during the A/H1N1 pandemic  
84 [10-11].

86 The inherent variability of new variants makes predictions difficult. Each pandemic  
87 virus has its own intrinsic properties which can evolve during the pandemic period. Then,  
88 intrinsic pathogenicity of new pandemic variants appears to be unpredictable. Data  
89 experimental derived from animal models must not be directly extrapolated to humans: in  
90 the A/H1N1 case, experiences with ferrets predicted a severity of pneumonia intermediate  
91 between that due to seasonal virus and the highly pathogenic avian H5N1 virus [12]. But in  
92 fact, the fatality rate of the novel A/H1N1 virus was relatively mild.

93 The novel 2009 H1N1 virus reminded the 1918 pandemic, also caused by a H1N1  
94 virus, despite totally distinct, which was associated with a large number of secondary  
95 bacterial co-infection which could explain partially the huge number of deaths [13]. Because  
96 of drastically different sanitary conditions nowadays, it is awkward to use the 1918 data as a  
97 basis for anticipating the spread, severity, and health consequences of present and future  
98 H1N1 pandemics. Currently, the use of antibiotics and anti-pneumococcal vaccines allow to  
99 efficiently combat the historically lethal bacterial co-infections. The availability of adapted  
100 vaccine and the rapid evolution on several domains such as antiviral therapeutics and

hygiene conditions are likely to play a critical role in the burden of these new pandemic variants as well as the increase of air traffic in their spread. Some models take into account the impact of human interventions such as vaccine/antiviral delivery, isolation of infected patients, school closure, halting air traffic and non-pharmaceutical interventions. Moreover, it remains often difficult to evaluate their real impact even without applying any model. For example, it was only in the late nineties that hand washing indisputably demonstrated, through randomized trials, its efficacy to prevent inter-human transmission in developed countries [14-15]. In 2005, a randomized-trial in Pakistan confirmed it in low-income countries [16]. Furthermore, the efficacy of mask use, largely recommended during A/H1N1 pandemic, to prevent respiratory infections is still to be clearly established by randomized trials [17-19]. Thereby, their introduction into models seems very tricky.

The vast majority of studies showed that immunization against influenza has a true impact in terms of hospitalization rate, global morbidity, influenza associated mortality as well as global mortality [20-26]. Intriguingly, during the immunisation campaign against the A/H1N1 pandemic virus, a large proportion of the population was reluctant to accept vaccination in some countries such as France and Germany. Human behaviours often are unpredictable and could vary among countries and vary with time. In France, the negative image provided by the mass media could have contributed to the low uptake of the A/H1N1 vaccine. We observed and reported that in public hospitals of Marseille, the nurses were less immunised against the new A/H1N1 pandemic virus than against seasonal flu [27]. Fears of vaccination promoted by anti-immunization lobbies are largely relayed by the media and the doubts induced and amplified by mediatization persists for a long time, even when scientists have demonstrated that there is no scientific evidence for suspicion. The association between multiple sclerosis and hepatitis B vaccine on one hand [28], and between autism and measles vaccine on the other hand [29] will be standing for many years to come, and any model is able to predict these events. One model can predict the willingness to accept a vaccine only for one specific situation. External factors cannot be included into models because they are often unknown until they appear. In France, the fact that medical information about the A/H1N1 vaccine was delivered and promoted primarily by politicians could have a counterproductive effect. Medical recommendations bypassing the medical system arouse suspicion in the population [27].

With hindsight, the recent pandemic reinforces the idea that presentation of pessimistic models mostly based on extrapolated hypotheses is deleterious. They impress governments and provoke fears. In another hand, it has been previously observed that pessimistic hypothesis about bioterrorism based only on speculations led governments to elaborate countermeasure plans with disproportionate measures. The Dark Winter operation, a bio-terrorist attack simulation, resembles movie script more than reality. Fears of a putative H5N1 avian flu pandemic amplified by pessimistic figures based on unsupported prediction constrained governments to implement emergency flu plans. Later on, these plans postulated that the fatality rate will be close to that observed in cases of A/H5N1 infection. For example, In France the 2009 emergency plan against pandemic flu predicted 91 000 to 212 000 deaths [1]. But A/H5N1 virus is still an almost pure zoonotic agent with transmission properties drastically distinct from those of the human adapted H1N1, H2N2 or H3N2 viruses. During the A/H1N1 pandemic in Marseille, no intermediate measure had been planified between (i) maintaining the organisation and logistics of the public hospital system as it was before the crisis, and (ii) the emergency opening of a 700 bed-hospital exclusively dedicated for A/H1N1 infected patients. In the real-life situation, along 10 month pandemic period, more than 2,500 clinical specimens were laboratory-documented: of these patients, around 11% were hospitalized and used simultaneously less than 50 beds at the peak of the pandemic.

In conclusion, infectious diseases remain unpredictable with mathematical models because pathogens and their ecosystem evolve continuously in a very unstable manner. Of course, some models which take into consideration the antiviral/antimicrobial therapies, the vaccines, the sanitary condition and the non-pharmaceutical interventions are useful to anticipate some logistic problems (quantity to purchase...) and can help to prepare the response to the future pandemics but they cannot predict with acceptable accuracy the major features of a future pandemic (number of cases, hospitalization, deaths...). The pessimistic predictions resulting from bioterrorism and the putative avian flu outbreak were published in highly-rated scientific journals. However they were neither supported by indisputable scientific evidence nor confirmed in real-time up to now. They fuelled fears in the population through amplification by the media, causing great concern amongst the public and the politicians. In order to fight future outbreaks and as a complementary

approach of modelling methods, we need to reinforce the network of sentinel centres by increasing their timely detection/diagnostics capacities and by implementing a large variety of technological tools detecting abnormal events. The data from these sentinel centres should not be necessarily exhaustive but they require to produce sufficient amount of data to investigate emergence and epidemic tendencies. Coupled with the fact that data from hospital-based surveillance systems and Google searching tools are easily and timely available, such surveillance method system will not be very costly. Our capacity for analysis and laboratory documentation needs to be increased and better integrated; during a crisis all data must be rapidly shared using communication media such as internet [30]. Rapid communication of research using specific free media such as Promed and 'PloS Currents: Influenza' can also improve the information dissemination. In addition, very early data about a new variant could be incorporate in some models and then produce more accurate predictions. Furthermore, decision process should be based on timely available scientific data to allow decision makers to take real time decision. Precautionary principle should be advantageously replaced by alertness principle.

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